Fabrication of Hydroxypropyl methylcellulose(HPMC) Resin-Fortified Poly(ethyl acrylate-co-methyl methacrylate) Nanoparticles Emulsion in Aqueous Medium

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A Master's Thesis
Submitted to the Department of Chemical Engineering
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Master of Chemical Engineering

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June 2008

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June 2008

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Fabrication of Hydroxypropyl methylcellulose(HPMC) Resin-Fortified Poly(ethyl acrylate-co-methyl methacrylate) Nanoparticles Emulsion in Aqueous Medium

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Copolymer [ethyl acrylate (EA): methyl methacrylate (MMA), 2:1] (Eugragit NE) is widely used in aqueous sustained release coating of pharmaceutical field. However, the film properties of copolymer [ethyl acrylate (EA): methyl methacrylate (MMA), 2:1] (Eugragit NE) is brittle and breakable so it needed to use plasticizer such as propylene glycol. To improve film properties of acryl copolymer, hydroxypropylmethylcellulose (HPMC) is used as a polymeric emulsifier in the redox polymerization in emulsion system of methyl methacrylate (MMA) and ethyl acrylate (EA).

The synthesis of HPMC resin fortified poly(EA-co-MMA) nanoparticles was carried out by ceric ammonium nitrate (CAN) induced redox polymerization in homogeneous aqueous medium.

These grafted copolymers were characterized by fourier transform infrared spectra (FTIR), scanning electron microscopy (SEM), differential scanning calorimeter (DSC), capillary hydrodynamic fractionation (CHDF) and dynamic light scattering (DLS) methods. The mechanical properties of grafted copolymer films were characterized by universal testing machine (UTM). In addition, the disintegration time of the grafted copolymer films was studied.

Keywords: HPMC-fortified • poly(EA-co-MMA) • CAN • resin fortified • sustained release

Ⅰ. INTRODUCTION

1. Poly(ethyl acrylate-co-methyl methacrylate, 2:1) (Eudragit NE)

Sustained release dosage forms deliver the active ingredient over up to 24 hours. The objective is to achieve a longer-lasting therapeutic effect with a medication that does not need to be taken as often and has fewer side effects [1, 2]. These factors improve patient compliance and safe administration of the medication, making the therapy more successful, especially for long term regimens. With sustained release dosage forms, the phase that determines the rate is the precisely controlled drug release, not the absorption phase. Preferably the active is absorbed as soon as it is released. In many cases, a zero order release profile is desired, to keep blood plasma levels as balanced as possible. In cases where a rapid increase of plasma level is desired, the drug is preferably separated into immediate and maintenance doses.

The reduced dosing frequency of sustained release dosage forms is generally accompanied by an increase of the single dosage of the drug. As a result, formulators need to consider more carefully drug safety and to limit the risk of dose-dumping [3]. Special consideration of the active's physical and chemical properties becomes more significant in the context of the development of sustained release dosage forms than with immediate release

formulations. Sustained release preparations is an advantageous way to treat any indication, e.g. cardiovascular diseases, pain management and diseases of the central nervous system.

Poly(ethyl acrylate-co-methyl msthacrylate, 2:1) (Eudragit NE) is a very soft material, and which shows a low glass transition temperature of 9°C and an minimum film-forming temperature (MFFT) of 5°C. Due to this softness, a large amount of anti-tacking agents are required. The neutral Eudragit NE polymer does not have any functional media independent of pH without dissolving [4]. Processing the polymers according to standard formulations produces the following relative permeability of the coatings [5].

Table 1. Properties and characteristics of Poly(ethyl acrylate-co-methyl methacrylate, 2:1) (Eudragit NE).

l Weight-average molar mass(M_w): ~800000 g/mole
l Glass transition temperature(T_g): ~9℃
l Minimum film-forming temperature(MFFT): ~5℃
l Water vapor transmission rate(WVTR): ~300 g/m^2d
l Tensile strength: 8 N/mm
l Elongation at break: 600%
l Nonionic(Neutral Ester)
l Permeable, not soluble
l pH-independent release
l No reactive functional groups
l Suitable cleaning agents: acetone, isopropyl alcohol, Ethanol or isopropyl alcohol/water 4:6

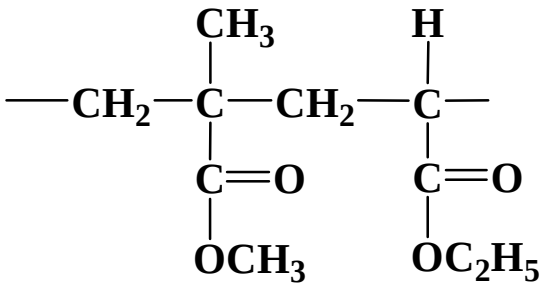


Fig. 1. Structural formula of Poly(ethyl acrylate-co-methyl msthacrylate, 2:1) (Eudragit NE).

2. General Description of Emulsion Polymerization

The emulsion polymerization method has many advantages over bulk and suspension polymerization system. Among these advantages are [6]:

(1) Emulsion polymerization gives much higher reaction rates and larger molecular weights than those obtained from either bulk or suspension polymerizations

(2) Since the product is in the form of a low viscosity dispersion commonly called a latex, it is easily handled in industrial fields

(3) Polymerization reactions are highly exothermic so thermal control of such reactions is a vital consideration. Heat dissipation problems are negligible in emulsion polymerization because the water, by virtue of its large heat capacity and low viscosity, acts as an efficient heat sink

(4) The solvent for this method is water, which is cheaper, far less dangerous and easier to handle than the organic solvents used extensively in bulk polymerizations. On the other hand, some disadvantages of the emulsion polymerization method are contaminants such as inorganic salts which can affect the properties of the final products and cost of separation process to obtain polymer solid

Chemical reactions in emulsion polymerization take place as in other types of polymerization; (1) initiation reaction; (2) propagation reaction; (3)

termination reaction; (4) chain transfer reaction.

Emulsion polymerization can be conveniently divided into three stages of separate intervals with respect to the concentration of polymer particles per milliliter of solution and the existence of a separate monomer phase [7, 8]. The various phases present in each of these three stages of polymerization are depicted in Fig. 2. Each stage can be characterized by changing R_p and the surface tension of the mixture as a function of percent conversion. Emulsion polymerization takes place in the interior of the micelles, which act as a meeting place for the organic monomer and initiator. When the monomer is added into an aqueous phase containing surfactant molecules, the hydrophobic ends of the surfactant surround the monomer droplet, and the hydrophilic ends of the surfactant will face toward the aqueous phase because, in contrast to the hydrophilic groups, hydrophobic ends are not water soluble [9].

Because monomer droplets act solely as reservoirs of monomer (essentially because their total surface area is so much less than that of particles), and the latex particles imbibe the monomer as it is polymerized within them, eventually the monomer droplets must become exhausted, at which point the droplet phase disappears. At this stage, the monomer will still be within the latex particles (and, to a far lesser extent, within the aqueous phase, the monomer in which is in thermodynamic equilibrium with that in the particles); hence polymerization will continue even though monomer droplets have

ceased to exist. It is convenient to divide emulsion polymerization into the three stages or Intervals as follows (see Table 2);

(1) *Interval I*: a rapid, transitory period in which emulsion polymerizations commence. It is characterized by an increasing rate of reaction primarily due to particle nucleation. This end when $dN_p/dt \rightarrow 0$.

(2) *Interval II*: this succeeds Interval I, and in a system commences when particle nucleation ceases. All three possible phases are present: an aqueous phase, latex particles and monomer droplets. Constant polymerization period is maintained during $d[M]_p/dt = 0$ on account of a balance arising between the free energy of mixing (polymer seeks to become infinitely dilute in monomer) and surface energy effects (limiting contact between swollen latex particles and the continuous phase).

(3) *Interval III*: this is the final stage of reaction. As polymerization progresses and monomer is consumed, the monomer droplets eventually become exhausted and disappear: Interval II ends and Interval III commences (sometimes conditions are such that a system goes straight from Interval I to Interval III: droplets disappear before particle formation has ceased). Only latex particles and the aqueous phase are present during this period, with the majority of the remaining monomer being confined to the latex particles, although a small amount (depending on the aqueous-phase solubility of the monomer) will be dissolved in the continuous phase.

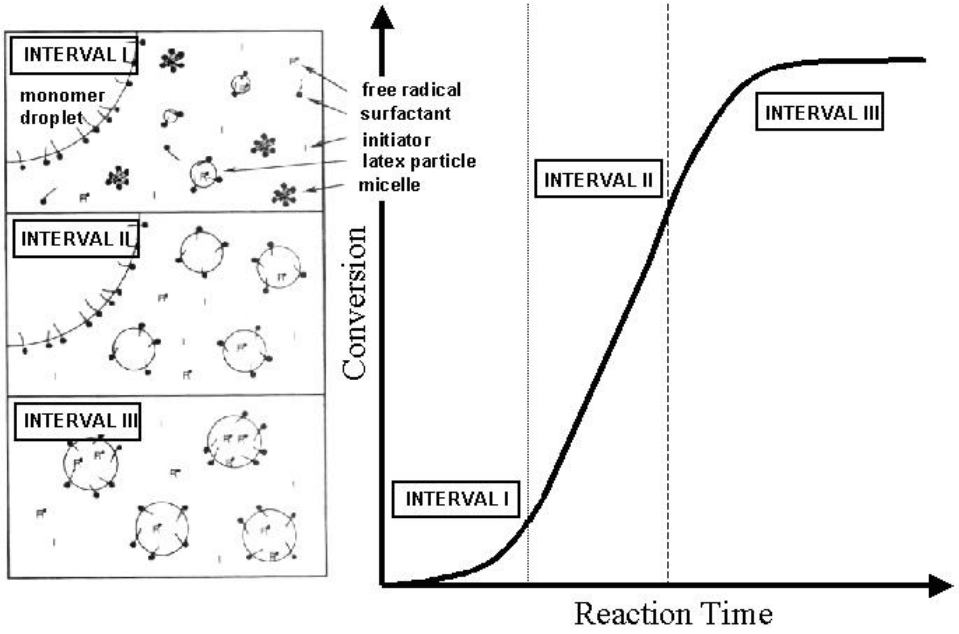


Fig. 2. The three intervals of an emulsion polymerization.

Table 2. Qualitative details of the three Intervals of emulsion polymerization [10]

Interval	Typical % Conversion	Micelles	Monomer Droplets	Particle Number	Particle Size	Comments
I	0 – 10	Present	Present	Increases	Increases	Nucleation period
II	10 – 40	Absent	Present	Constant	Increases	$[M]_p$ [a)] constant
III	40 - 100	Absent	Absent	Constant	Roughly Constant	$[M]_p$ decreases

[a)] Monomer concentration in latex particles

3. Free-radical grafting

Using twin screw extruders as reactors, the reactive extrusion process can be carried out to obtain polymers and realize continuous extrusion. Its application mainly involves in situ polymerization, crosslinking, chemical modification, and blending [11-15]. Modification of polymer, which is aimed to bring chemical changes that can improve the properties, has been developed rapidly in recent years. In addition, grafting by reactive extrusion is one of the most prevalent methods for introducing functional groups into polymers [16-20].

Reactive extrusion process is very complicated because of the considerable coupling variables involved such as, fluid flow, heat transfer and chemical reaction. In order to quantitatively analyze the reaction behavior and optimize the processing conditions, investigation via numerical simulations has become an active research object. Polyolefins are the most common polymers modified by grafting reactions. Motha and Seppala developed a general kinetic model to simulate the grafting of monomers, such as unsaturated carboxylic acids and silanes, to ethylene polymers in a single screw extruder [21]. Hojabr et al. mathematically studied the melt grafting of glycidyl methacrylate onto polyethylene in a co-rotating twin screw extruder. Fukuoka built a computer simulation for the grafting of polyolefins with vinyl monomers in a self-

wiping co-rotating twin screw extruder on the basis of the reaction kinetics and rheological models. The profiles of local pressure, filling factor, cumulative residence time, temperature, reaction conversion and shear viscosity were presented [15, 22]. White et al. proposed kinetic models of free radical grafting with maleic anhydride, styrene and methyl methacrylate onto polypropylene, and then combined these with models for polymer degradation, fluid mechanics and heat transfer, mathematically simulated the grafting reactions of maleic anhydride and methyl methacrylate onto polypropylene in modular co-rotating twin screw extruders [23-25].

In the chemical process, free radicals are produced from the initiators and transferred to the substrate to react with monomer to form the graft copolymers. In general, one can consider the generation of free radicals by indirect or direct methods [26].

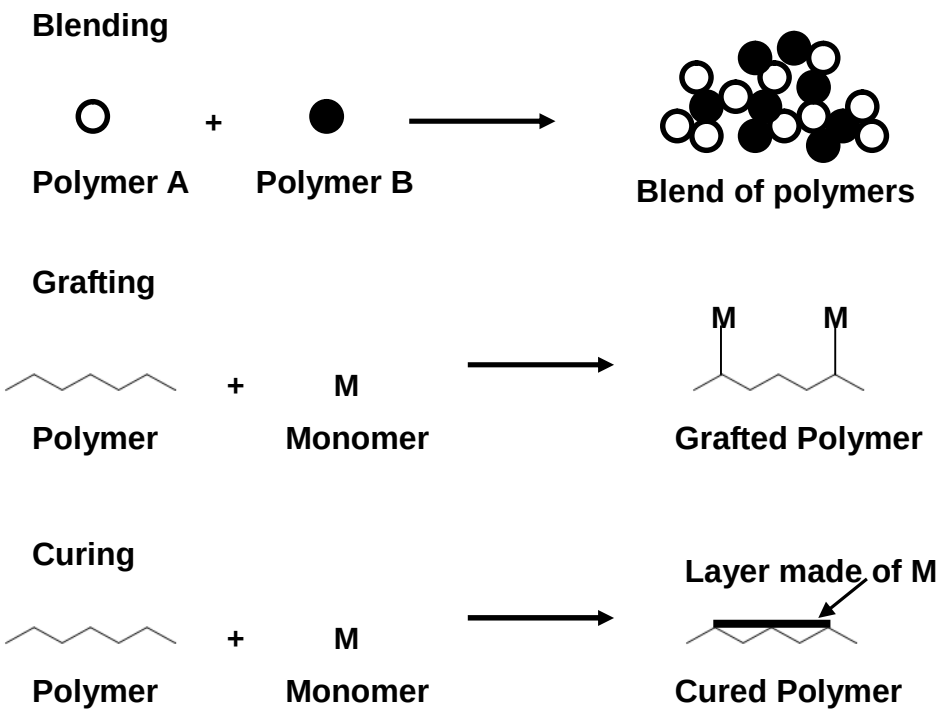


Fig. 3. Schematic representation of the methods of polymer modification.

The materials in the reactive extrusion process for grafting primarily involve the molten polymer, monomer or mixture of monomers and initiator. When the polymer is initiated by the initiator, a polymer free radical is generated; the monomer is then grafted to the polymer backbone. Grafting modification of polyolefins is often accompanied by side reactions such as the homopolymerization of monomers, crosslinking or even degradation of polymer chains [18, 27, 28].

As mentioned above, the chemical reactions in the reactive extrusion process for the grafting modification of polyolefins are so complex that it is necessary to introduce some simplifying assumptions and approximations. For the grafting reaction of vinyl monomers onto polyethylene, the homopolymerization of the monomer is not included because of the low monomer concentration, and the termination reaction involving the graft polymer radicals is neglected because of the high chain transfer coefficient. So the elementary reactions are shown as follows [15]:

(1) Decomposition of initiator $I \xrightarrow{k_d} 2R\cdot$

(2) Initiation of polymer $R\cdot + P \xrightarrow{k_i} RH + P\cdot$

(3) Monomer graft onto polymer radical $R\cdot + M \xrightarrow{k_g} PM\cdot$

(4) Intermolecular transfer to polymer $PM\cdot + P \xrightarrow{k_{tr}} RMH + P\cdot$

(5) Termination reaction $P\cdot + P\cdot \xrightarrow{k_{tr}} P\text{-}P$

where I, M and P represent the initiator, monomer and base polymer, respectively; R·, P· and PM· represent the primary free radical, base polymer radical and graft polymer radical, respectively; PMH and P-P represent the graft polymer and crosslinking polymer, respectively; and, k_d, k_i, k_g, k_{tr} and k_t denote the rate constants for initiator decomposition, polymer initiation, monomer grafting, radical transfer and termination, respectively.

4. Cellulose Polymer

Cellulose is one of many polymers found in nature. Wood, paper, and cotton all contain cellulose. Cellulose is an excellent fiber. Wood, cotton, and hemp rope are all made of fibrous cellulose. Cellulose is made of repeat units of the monomer glucose. This is the same glucose which your body metabolizes in order to live, but you can't digest it in the form of cellulose. Because cellulose is built out of a sugar monomer, it is called a polysaccharide.

Cellulose is an organic compound with the formula $(C_6H_{10}O_5)n$, a polysaccharide consisting of a linear chain of several hundred to over ten thousand $\beta(1\rightarrow4)$ linked D-glucose units [29, 30].

Cellulose is the structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. Some species of bacteria secrete it to form biofilms. Cellulose is the most common organic compound on Earth. About 33 percent of all plant matter is cellulose (the cellulose content of cotton is 90 percent and that of wood is 50 percent) [31].

For industrial use, cellulose is mainly obtained from wood pulp and cotton. It is mainly used to produce cardboard and paper; to a smaller extent it is converted into a wide variety of derivative products such as cellophane and rayon.

Some animals, particularly ruminants and termites, can digest cellulose

with the help of symbiotic micro-organisms that live in their guts. Cellulose is not digestible by humans and is often referred to as 'dietary fiber' or 'roughage', acting as a hydrophilic bulking agent for feces.

Cellulose was discovered in 1838 by the French chemist Anselme Payen, who isolated it from plant matter and determined its chemical formula [29, 32]. Cellulose was used to produce the first successful thermoplastic polymer, celluloid, by Hyatt Manufacturing Company in 1870. Hermann Staudinger determined the polymer structure of cellulose in 1920. The compound was first chemically synthesized (without the use of any biologically-derived enzymes) in 1992, by Kobayashi and Shoda [33].

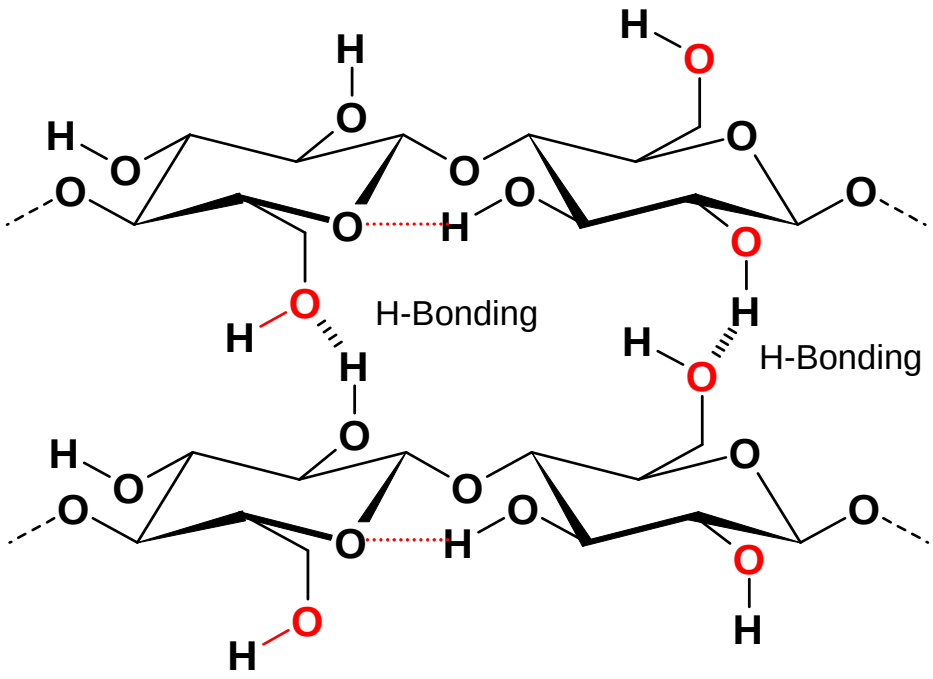


Fig. 4. Structure of cellulose.

4.1. Hydroxypropyl methylcellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC), is a semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products [34, 35].

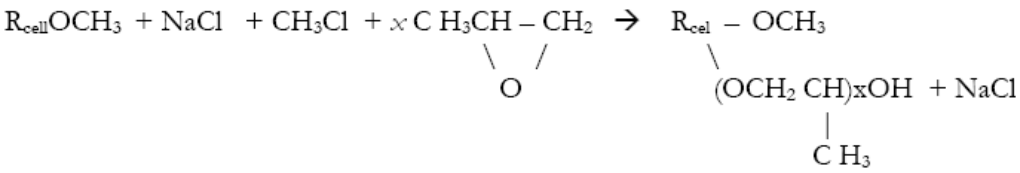
HPMC solutions were patented as a semisynthetic substitute for tear-film. Its molecular structure is predicated upon a base celluloid compound that is highly water soluble. Post-application, celluloid attributes of good water solubility reportedly aids in visual clarity. When applied, a HPMC solution acts to swell and absorb water, thereby expanding the thickness of the tear-film. HPMC augmentation therefore results in extended lubricant time presence on the cornea, which theoretically results in decreased eye irritation, especially in dry climates, home, or work environments [36]. On a molecular level, this polymer contains beta-linked D-glucose units that remain metabolically intact for days to weeks. On a manufacturing note, since HPMC is a vegetarian substitute for gelatin, it is slightly more expensive to produce due to semisynthetic manufacturing processes. Aside from its widespread commercial and retail availability over the counter in a variety of products, HPMC 2% solution has been documented to be used during surgery to aid in corneal protection and during orbital surgery.

HPMC is considered to be part of the group of compounds know as cellulose ethers. See the TAP review for cellulose for details of cellulose manufacturing, as well as the process for manufacture of microcrystalline cellulose (MCC). Many derivatives have been developed from cellulose, involving more drastic chemical modification of the basic cellulose molecule [37]. Various reaction products with methyl chloride are known as the methyl celluloses. This group includes carboxymethylcellulose (CMC) or cellulose gum; hydroxypropyl methylcellulose (HPMC) or carbohydrate gum; and methyl cellulose or modified vegetable gum [38]. Methlycellulose is derived from alkali cellulose reacted with methyl chloride that adds methyl ether groups. The MC is then also reacted with

propylene oxide to form HPMC. Other methyl cellulose derivatives include hydroxyethylmethylcellulose (HEMC), and hydroybutylmethylcellulose (HBMC) [38, 39]. The cellulose ethers are manufactured by a reaction of purified cellulose with alkylating reagents (methyl chloride) in presence of a base, typically sodium hydroxide and an inert diluent. The addition of the base in combination with water activates the cellulose matrix by disrupting the crystalline structure and increasing the access for the alkylating agent and promotes the etherification reaction. This activated matrix is called alkali cellulose [39]. During the manufacture of HPMC alkali cellulose reacts with methyl chloride to produce methyl cellulose and sodium chloride. Side

reactions of the methyl chloride and sodium hydroxide produce methanol and dimethyl ether by-products. The methylcellulose is then further reacted with the staged addition of an alkylene oxide, which in the case of HPMC is propylene oxide [39, 40]

$$R_{cell}OH{:}NaOH + CH_3Cl \rightarrow R_{cell}OCH_3 + NaCl \quad (1)$$



After this reaction, MC and HPMC are purified in hot water, where they are insoluble. Drying and grinding completes the process.

Cellulose quality is measured by the content of alpha-cellulose, which is that portion insoluble in 18% alkali. Highly purified forms (over 99% alpha cellulose) are used to make the derivatives such as the cellulose gums, including sodium carboxymethylcellulose, methylcellulose and hydroxypropylmethylcellulose.

Methyl chloride (CH_3Cl) is colorless gas with a faint, sweet odor that is not noticeable at dangerous concentrations. Synthetic forms are a chlorinated hydrocarbon derived from petroleum, and a suspected carcinogen [41]. It is also generated from incineration of municipal and industrial waste; though natural sources primarily oceans and biomass burning constitutes most of the

global release into the environment [42].

Propylene oxide is also a petroleum derivative, with a large volume and importance in the polyurethane and surfactant industry [43]. There are two principal processes used: the traditional chlorohydrin process and indirect oxidation by the hydroperoxide process that uses a molybdenum catalyst. Both processes start with propylene (propene) derived from cracking of petroleum. The chlorhydrin process involves reaction of propylene ($CH_3CH=CH_2$) and chlorine in the presence of water to produce two isomers of propylene chlorhydrin. This is followed by dehydrochlorination using caustic soda or lime to produce propylene oxide and salt. The hydroperoxide process involves oxidation of propylene to PO by an organic hydroperoxide, producing an alcohol as a co-product. One of the possible alcohols (tert-butanol, TBE) produced as a by-product from this process is used as feedstock for MTBE, a gasoline additive [43].

Table 3. Properties and characteristics of HPMC.

- White or yellowish white powder
- Soluble in water and mixed organic solvent
- Making up transparent film when solvent remove
- Using for DDS (Drug Delivery System) to control the drug effect rate in appearance time depending on the property of regular dissolution wide range of pH(2~13)
- No chemical reaction with drug due to its non-ionic property
- CAS Number: 9004-65-3
- Molecular weight: 10,000~1,500,000
- Melting point: 190~230℃(Tg 170~180℃)
- Gel point: 50 ~ 90℃
- Auto-ignition point: 360℃
- Application Fields: Pharmaceutical, Food, Cosmetics, Personal Care

In this study, to improve film properties of poly(EA-co-MMA), hydroxypropyl methylcellulose (HPMC) was used and investigated as a polymeric emulsifier in the redox polymerization in emulsion system of [44] ethyl acrylate (EA) and methyl methacrylate (MMA). The HPMC-g-poly(EA/MMA) can be applied to sustained release coating. The synthesis of HPMC-g-poly(EA/MMA) was carried out with ceric ammonium nitrate [42] induced redox polymerization in homogeneous aqueous medium.

Ⅱ. EXPERIMENTAL

1. Materials

Following raw materials were used to prepare HPMC-g-poly(EA/MMA). Hydroxypropyl methylcellulose (HPMC) powders were provided by Samsung Fine Chemical Co. Ltd. (Korea). Ethyl acrylate (EA) and methyl methacrylate (MMA) were obtained from Junsei Chemical. Sodium lauryl sulfate (SLS) was bought from Duksan Pure Chemical. Ceric ammonium nitrate (CAN) was purchased from Aldrich Chemical. Double-distilled and deionized (DDI) water was used all through the experiment. All reagents were used without further purification except MMA. In the case of MMA, inhibitor in MMA was purified by passage through the inhibitor Remover column (for removing HQ and MEHQ, Aldrich Co.); the purified monomers were subsequently stored at 0℃ until use.

2. Synthesis of HPMC-g-poly(EA/MMA)

HPMC-g-poly(EA/MMA) were synthesized in 500mL double-wall jacketed glass reactor equipped with a mechanical stirrer, a reflux condenser, a circulator and a nitrogen inlet. The reaction temperature was adjusted at 65±1℃ and the stirring rate was 250 rpm all through the reaction. In the reactor, 15 gram of HPMC and 3 gram of SLS were dissolved in DDI water at 65°C under N_2 atmosphere. The 0.4 gram of CAN was dissolved in the remaining water and added to the reactor. After 4 minutes, EA (3.3-16.7 gram) and MMA (1.7-8.3 gram) were added at a rate of 4.8~5.0 ml/min, and then the reaction was started right away. In general, polymerization proceeded for 4 hours or above in this work. Basic recipes for the preparation of HPMC-g-poly(EA/MMA) in each case were shown in Table 4 and reactor systems was given in Fig 5.

The used HPMC was substituted with four OH groups in each unit. This study used four concentrations of CAN. Among these four OH groups in HPMC one, two, three and four OH group should be oxidized by proper amount of CAN. CAN is activated in acid. The concentration in which CAN is the most activated is found by controlling the amount of nitric acid.

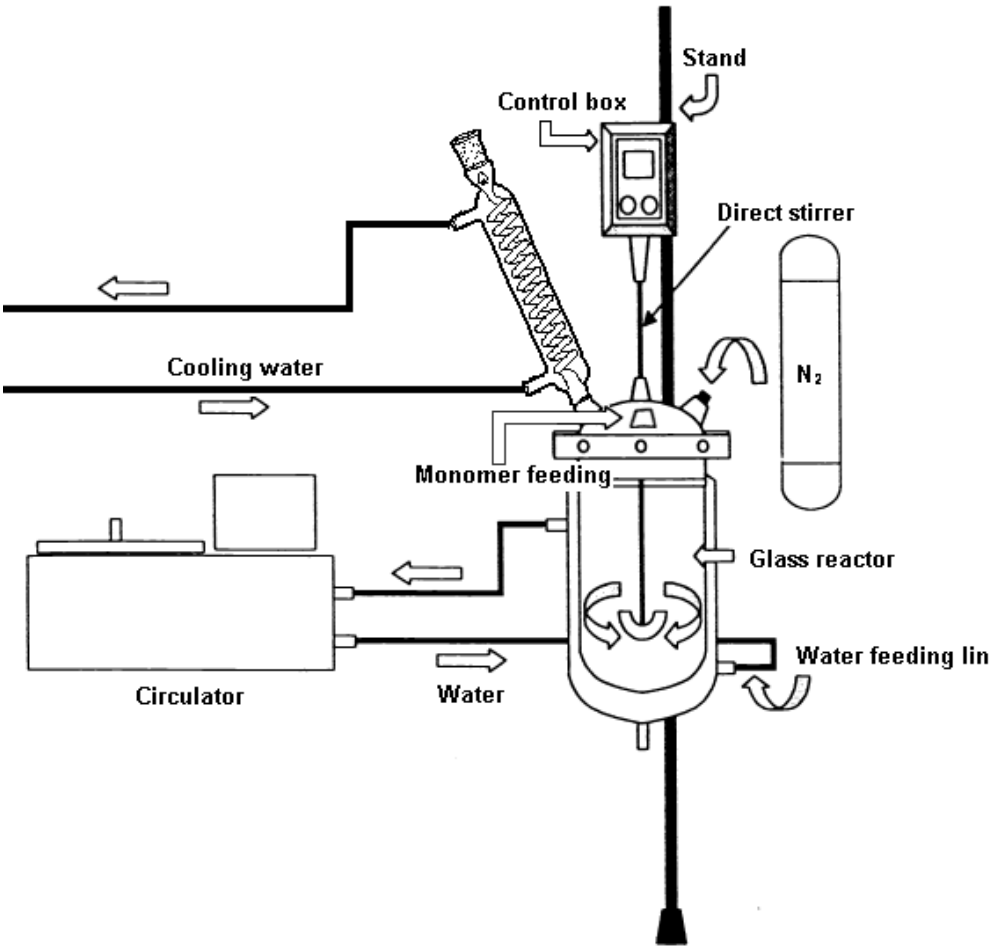


Fig. 5. Glass reactor system equipped with a circulator, a reflux condenser, nitrogen inlet, and direct stirrer.

Table 4. Basic recipe for emulsion polymerization of HPMC-g-poly(EA/MMA).

	Ingredients		Amount (g)
Reactor charge	HPMC		15
	DDI water		155
	SLS		0, 3, 5
Monomer mixture	MMA	Wt.%[a)]	11.3, 22, 33.3, 44.7, 55.3
		Amount (g)	1.7, 3.3, 5, 6.7, 8.3
	EA	Wt.%[a)]	22, 44.7, 66.7, 88.7, 111.3
		Amount (g)	3.3, 6.7, 10, 13.3, 16.7
Initiator solution	CAN		0.4, 0.8, 1.2, 1.6
	1mol/L HNO_3		0, 0.3, 0.5, 0.7, 1

a) Based on the HPMC contents

3. Characterization

3.1. Critical aggregate concentration (CAC)

HPMC-g-poly(EA/MMA) were polymerized with various concentration of monomer(ethyl acrylate, methyl methacrylate). The nanoparticles were dissolved in DDI water to prepare a 10wt% solution, which was then diluted in series. After dissolving pyrene in these solutions, the UV–Visible absorption spectra of these solutions were obtained with a UV–Visible spectrophotometer (UV-1601PC, Shimadzu).

3.2. Rate of polymerization

The monomer conversion was calculated by the gravimetric method using 100ppm of hydroquinone methanol solution as a quencher. Latex samples obtained from the reactor were immediately quenched with 2-3 drops of the inhibiting solution and then cooled down after the predetermined time of polymerization. The maximum rate of polymerization ($\boldsymbol{R_{p,max}}$) was calculated from the slopes of fractional conversion at 0.43.

3.3. Particle morphology

The morphology of the HPMC-g-poly(EA/MMA) was observed with a scanning electron microscopy (SEM, JSM-6500F, JEOL).

3.4. Thermal property analysis

A differential scanning calorimeter (DSC Q10, T.A. Instruments., USA) was used to examine the glass transition temperature (T_g) variations with the EA and MMA. The heating rate was 10 ℃min^{-1} under an N_2 purge of 30 mL min^{-1}. The sample size was 10mg in a sealed aluminum pan. DSC data were obtained from -30 to 450 ℃.

3.5. Particle size and particle size distribution

The average particle size and distribution of the latex particles were analyzed by capillary hydrodynamic fractionation (CHDF2000, Matec Applied Sciences., USA) and dynamic light scattering (DLS, 3000HAS, Malvern, UK).

$$\overline{D}_n = \frac{\sum N_i D_i}{\sum N_i} \quad (2)$$

The average particle size was obtained from the capillary hydrodynamic fractionation. The polydispersity index (PDI) was given as D_w/D_n, where D_w is the weight average diameter and D_n is the number average diameter of latex particles.

3.6. Mechanical property

Tensile properties and hardness of the dispersion-cast films were measured using a universal tensile machine (UTM, LR 10K, Lloyd) at a crosshead speed of 0.1 m min^{-1}. Sample specimens were prepared from the films with a 10 mm X 40 mm die, and the grip distance was set at 30 mm. The thicknesses of the films were between 0.1 mm and 0.3 mm. For each film, five specimens were tested and the average value was reported.

3.7. Dissolution profile at water

The Dissolution test of HPMC-g-poly(EA/MMA) was coated at aspirin tablets. Dissolution studies were conducted using a PTWS (Pharmatest, Germany) at a rotation speed of 50 rpm at 37±0.5℃. The dissolution media used were water. Fig 6 shows the general tablet coating process.

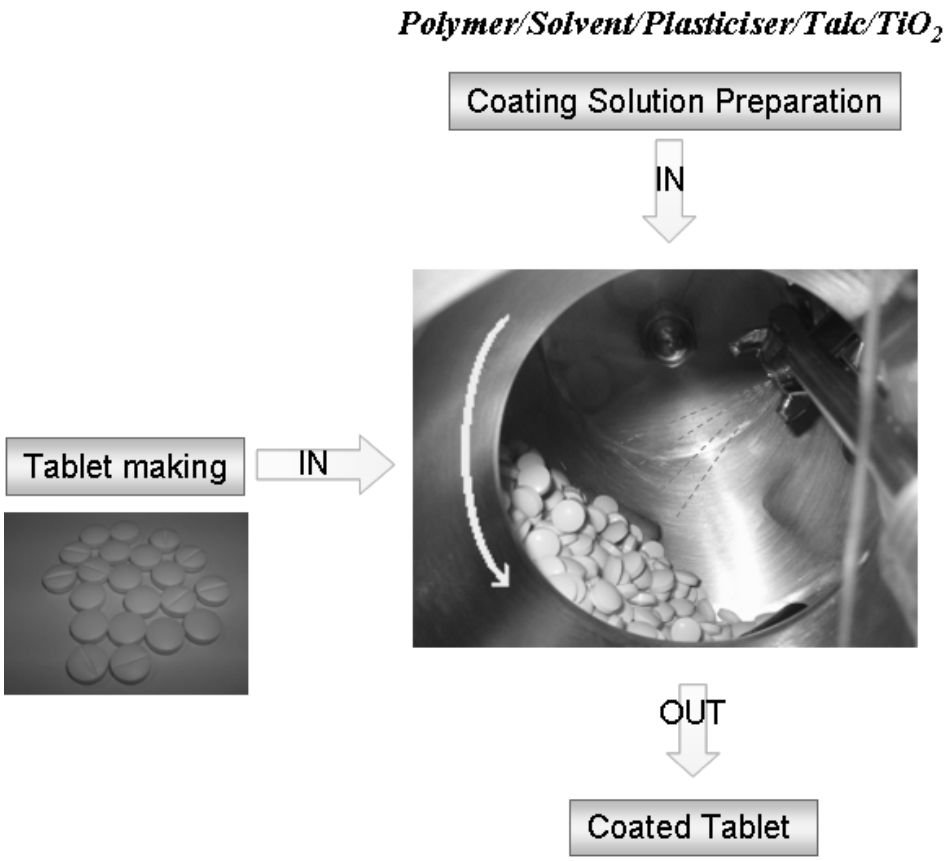


Fig. 6. General tablet coating process.

Ⅲ. RESULTS AND DISCUSSION

1. Synthesis of HPMC-g-poly(EA/MMA)

1.1. Effect of ceric ammonium nitrate (CAN)

Fig. 7. shows the final conversion curves of EA-co-MMA emulsion polymerization using four concentrations of CAN. Among these four OH groups in HPMCP, the one, two, three, and four-OH groups should be oxidized by proper amount of CAN.

When just one OH group is oxidized, the final conversion rate of the reaction has the highest value. When the two or more OH groups are oxidized, hydrophobic chains are generated on two or more sides which give rise to aggregation and restraint of chain-growth.

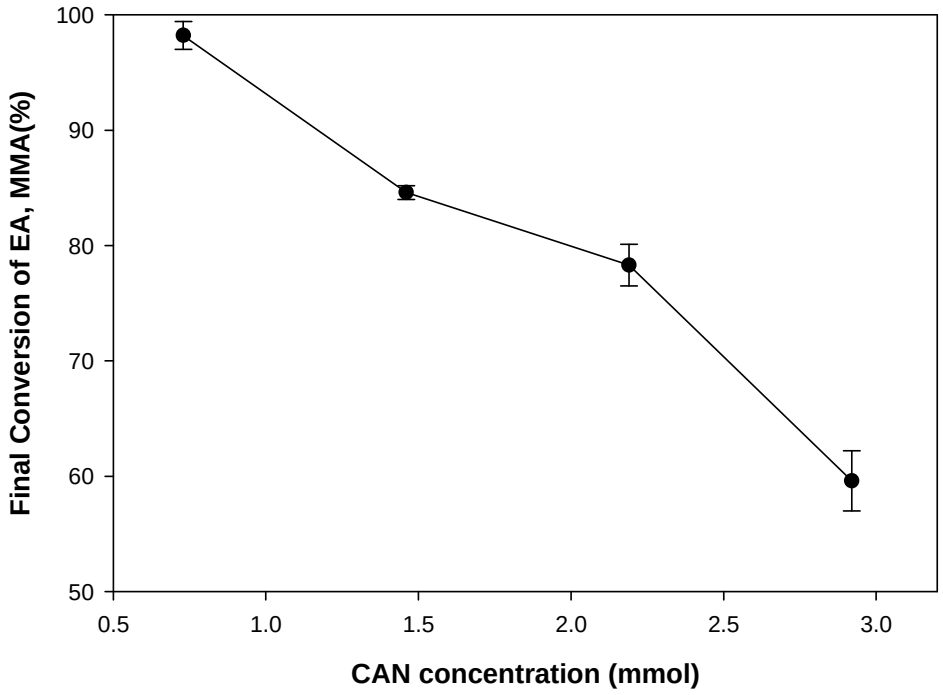


Fig. 7. Final conversion of emulsion polymerization of EA-co-MMA as a function of CAN concentrations.

1.2. Effect of nitric acid (HNO_3)

Fig. 8. shows the final conversion curves of EA-co-MMA emulsion polymerization using five concentrations of nitric acid. CAN is activated in acid. The concentration which activates CAN the most is found by controlling the amount of nitric acid. Nitric acid changes pH and CAN is activated. When CAN is activated 100%, it oxidizes the exact quantity of OH groups. When using 0.5g of 1mol/L nitric acid, the conversion rate of the reaction has the highest value.

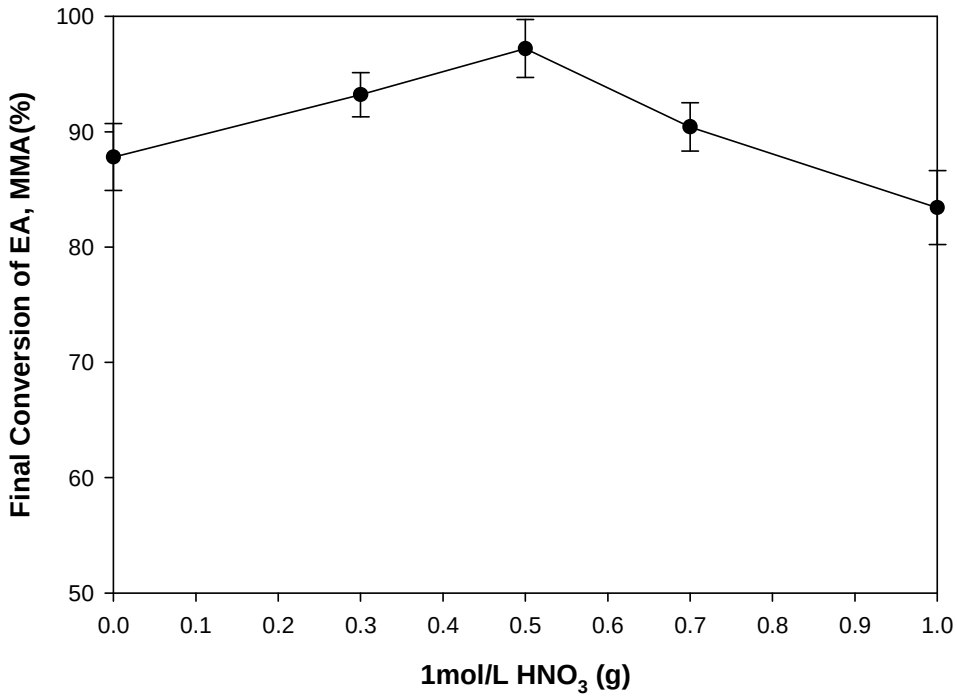


Fig. 8. Final conversion of emulsion polymerization of EA-co-MMA as a function of nitric acid concentrations.

1.3. Effect of sodium lauryl sulfate (SLS)

Fig. 9. shows the final conversion curves of EA-co-MMA emulsion polymerization using three concentrations of sodium lauryl sulfate (SLS).

The amount of SLS used is lower than CMC. A small quantity of SLS acts as a stabilizer. When the amount of SLS is lower than CMC, the amount of SLS has little relation to the conversion rate, but nevertheless when no SLS is added, very little conversion takes place.

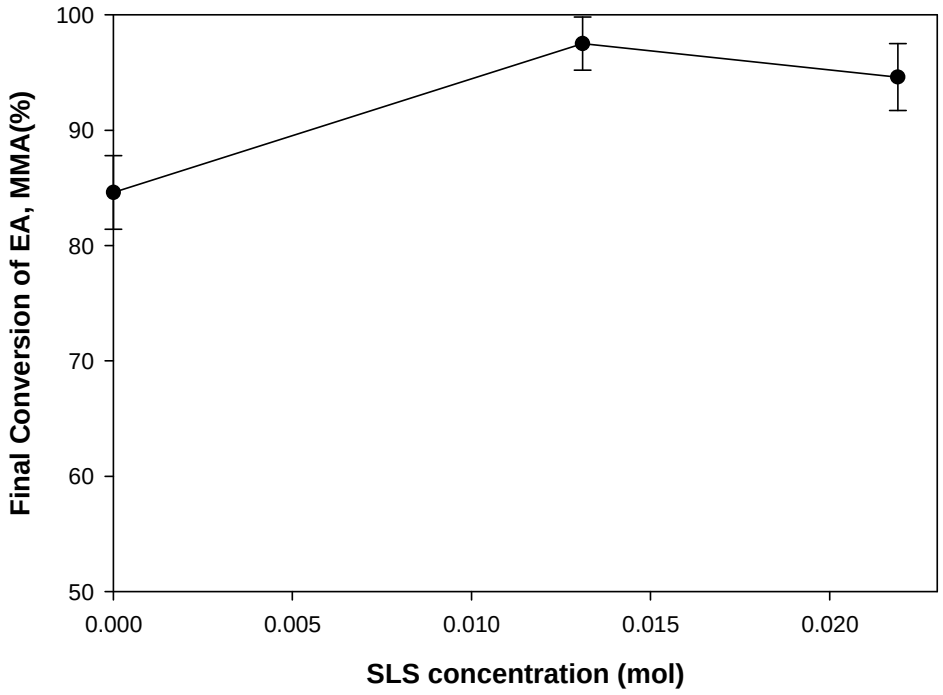


Fig. 9. Final conversion of emulsion polymerization of EA-co-MMA as a function of SLS concentrations.

1.4. Critical aggregate concentration (CAC) of HPMC-g-poly(EA/MMA)

Fig. 10. shows the CAC of HPMC-g-poly(EA/MMA). HPMC-g-poly(EA/MMA) were polymerized with various concentration (0.01mol-0.29mol, every 0.02mol) of monomer(EA and MMA). The nanoparticles were dissolved in DDI water to prepare a 10wt% solution, which was then diluted in series. After dissolving pyrene in these solutions, the UV–Visible absorption spectra of these solutions were obtained with a UV–Visible spectrophotometer.

The hydrophobic portion increased with increasing EA and MMA. When the hydrophobic portion increased, the CAC decreased. But when more than 0.07mol of monomer was added, on the other hand, there was little change in the number of micelles produced.

Among these four OH groups in HPMCP, only one OH group should be oxidized by a proper amount of CAN before adding MMA and EA. In response to the attaching of a monomer to oxidized O− in HPMC, the hydrophobic portion would increase so that it enables HPMC to form micelle. When the amount of HPMC is lower than that of CAC, HPMC will not be able to independently form micelles. When the MMA and EA remaining in water penetrate into the micelle, particles formed. (Scheme 1)

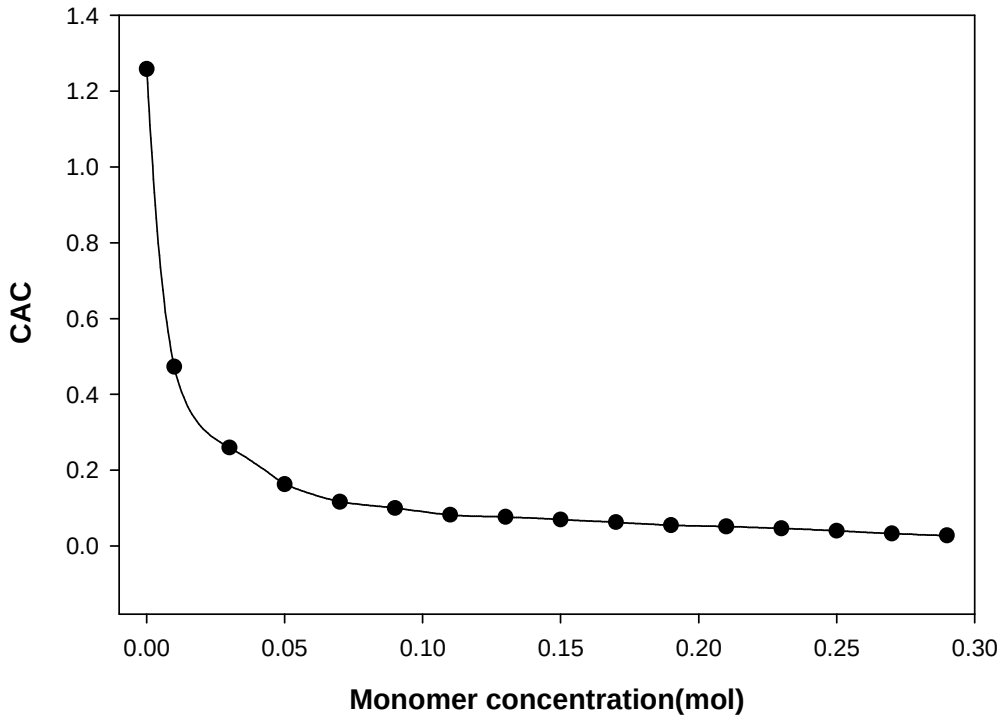
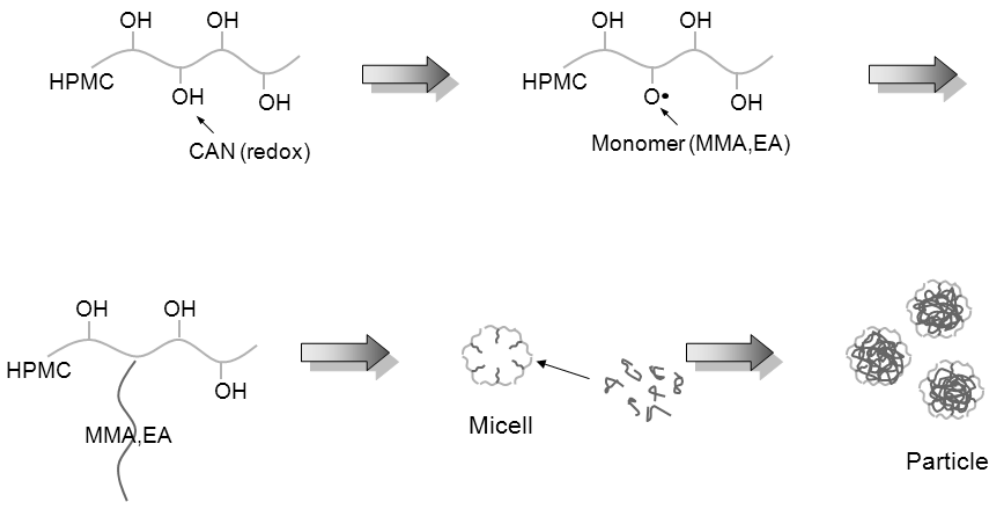


Fig. 10. CAC of HPMC-g-poly(EA/MMA).



Scheme 1. Schematic representation a process for the preparation of HPMC-g-poly(EA/MMA).

2. Characterization of HPMC-g-poly(EA/MMA)

2.1. Emulsion polymerization of EA and MMA with HPMC

Fig. 11. shows the time-conversion curves of the HPMC-g-poly(EA/MMA). Conversion rates increased rapidly for the first 90 minutes, but after that, the rate leveled off. The conversion rate reached its highest value at 0.25mol of monomer.

Unlike conventional emulsion polymerizations, the rate of polymerization in emulsion polymerizations with polymeric surfactant continues to increase in "Interval II" (by Harkins et al.), but at a lower rate, as does the number of particles. The end of this interval can be defined by the maximum rate of polymerization. "Interval III" starts at 40–50% conversion, during which the number of particles is constant and the rate of polymerization decreases [45]. Therefore, we chose the conversion at 0.43 as the point for calculation of the maximum polymerization rate, $R_{p,max}$, which are listed in Table 5.

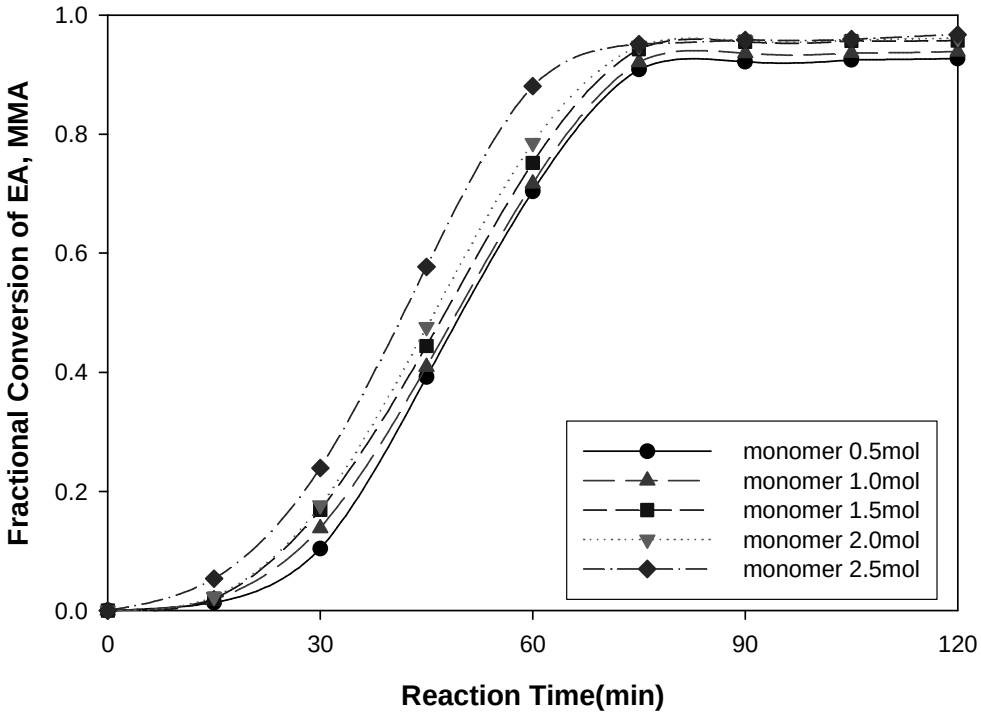


Fig. 11. Conversion profile of HPMC-g-poly(EA/MMA).

Table 5. $R_{p,max}$ value of HPMC-g-poly(EA/MMA).

Monomer (mol)	$R_{p,max}$ (10^{-4} M s^{-1}) [a)]
0.05	0.362
0.10	0.672
0.15	0.820
0.20	1.204
0.25	1.603

[a)] $R_{p,max}$ was calculated from the linear slope of the fractional conversion (~0.43) of EA and MMA

2.2. FT-IR spectra of the HPMC and HPMC-g-poly(EA/MMA)

FT-IR spectra of the HPMC and HPMC-g-poly(EA/MMA) are presented in Fig. 12. The CH_2 peak in the 2950-2980 cm^{-1} range was used as an internal standard. After completion of the reaction, the intensity of the OH peak at 3100-3600 cm^{-1} confirmed that, of the four OH groups in HPMCP, only one should be oxidized by proper amount of CAN. Appearance of the C=O absorption peak at 1650-1755 cm^{-1} in FT-IR spectrum indicates a reaction with monomer(EA and MMA) and O^- radical.

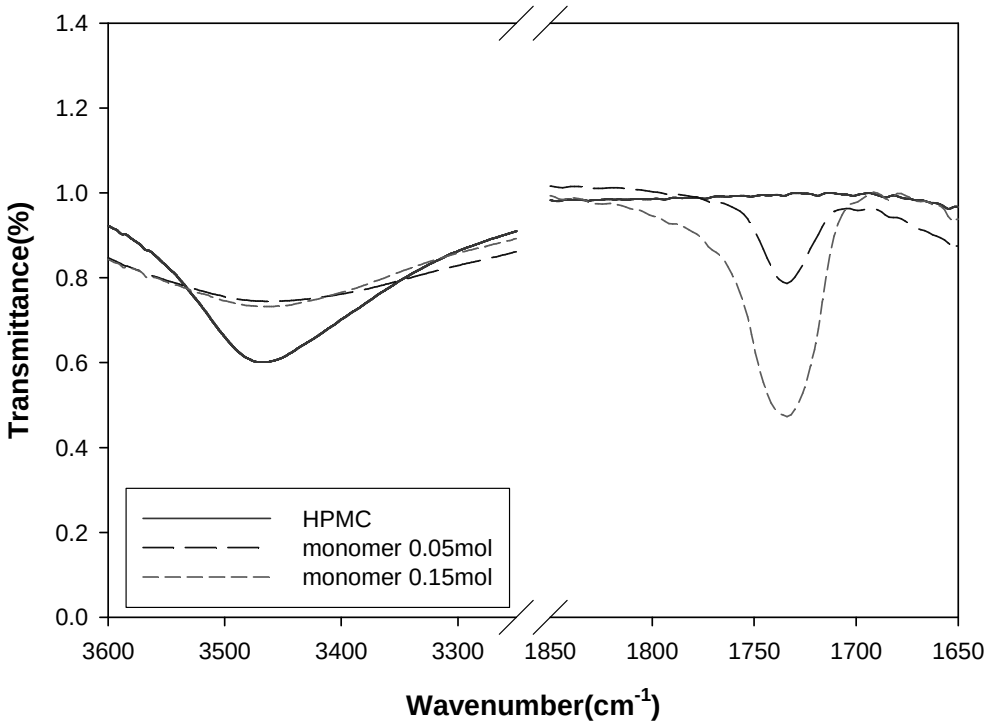


Fig. 12. FT-IR spectra of HPMC resin fortified poly(EA-co-MMA) and HPMC.

2.3. Thermal property analysis

The glass transition temperature of HPMC-g-poly(EA/MMA) was measured by a differential scanning calorimeter (DSC). Fig 13. shows the glass transition temperature of HPMC-g-poly(EA/MMA). According to this data, the glass transition temperature decreases as the amount of added monomer increases, because the glass transition temperature of poly(EA-co-MMA) is much lower than HPMC. The glass transition temperature of HPMC is 170-180 ℃. The glass transition temperature of poly(EA-co-MMA) is 9 ℃.

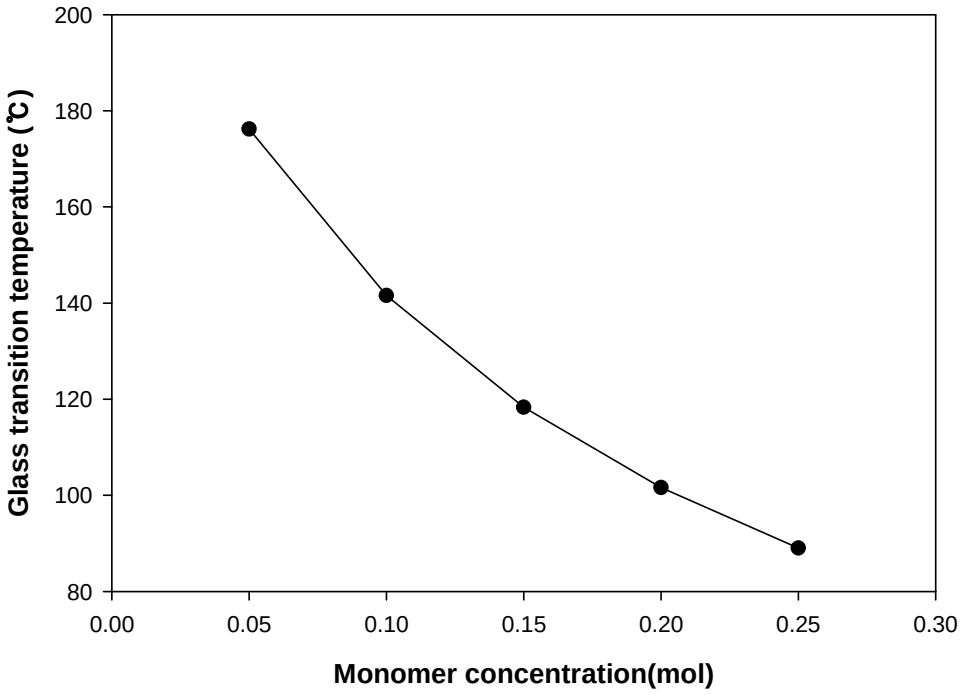


Fig. 13. Glass transition temperature of HPMC-g-poly(EA/MMA).

2.4. Particle size and particle morphology

Fig. 14. shows the number average of particle size and PDI of the HPMC-g-poly(EA/MMA). When 0.05mol of monomer was added, particle size was remarkably small because the monomer was consumed by forming micelles. When more than 0.07mol of monomer was added, on the other hand, there is little change in the number of micelles due to the regular CAC. In this case, the more monomer that was added, the bigger the particle that was formed because the monomer is used for making particles. When the amount of added monomer is 0.05mol, particles don't have sufficient monomer to grow.

From (A) to (C) in Fig. 15, showed SEM image of the HPMC-g-poly(EA/MMA). SEM micrographs showed that in all cases the particles exhibited a spherical shape, although diameters of the nanoparticles were slightly different. This result agreed well with the CHDF and DLS data.

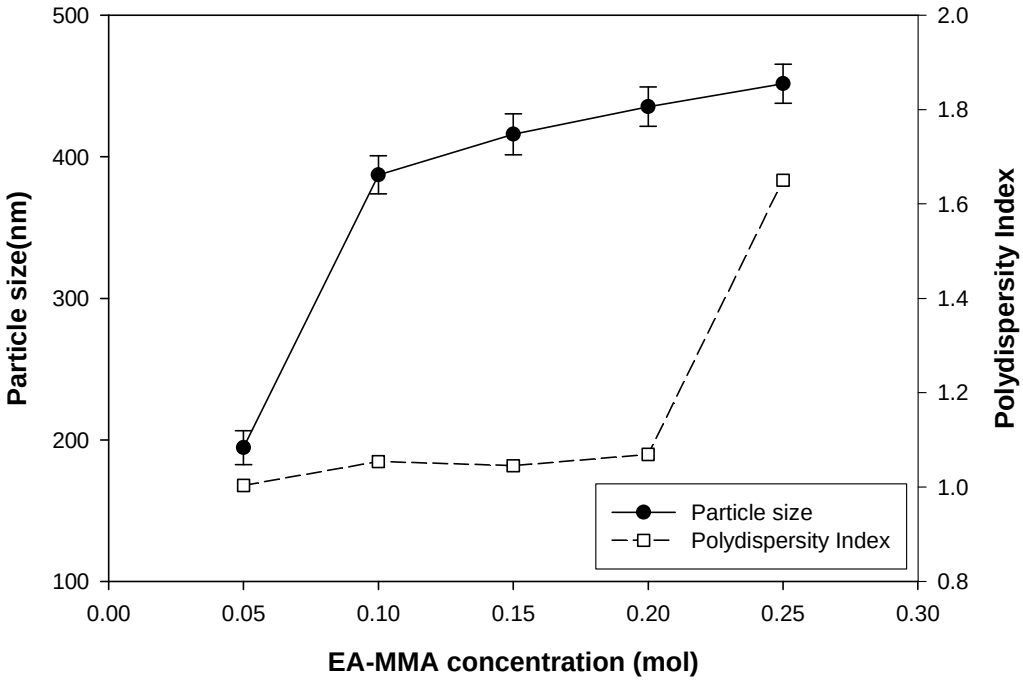


Fig. 14. Particle size and PDI of HPMC-g-poly(EA/MMA)

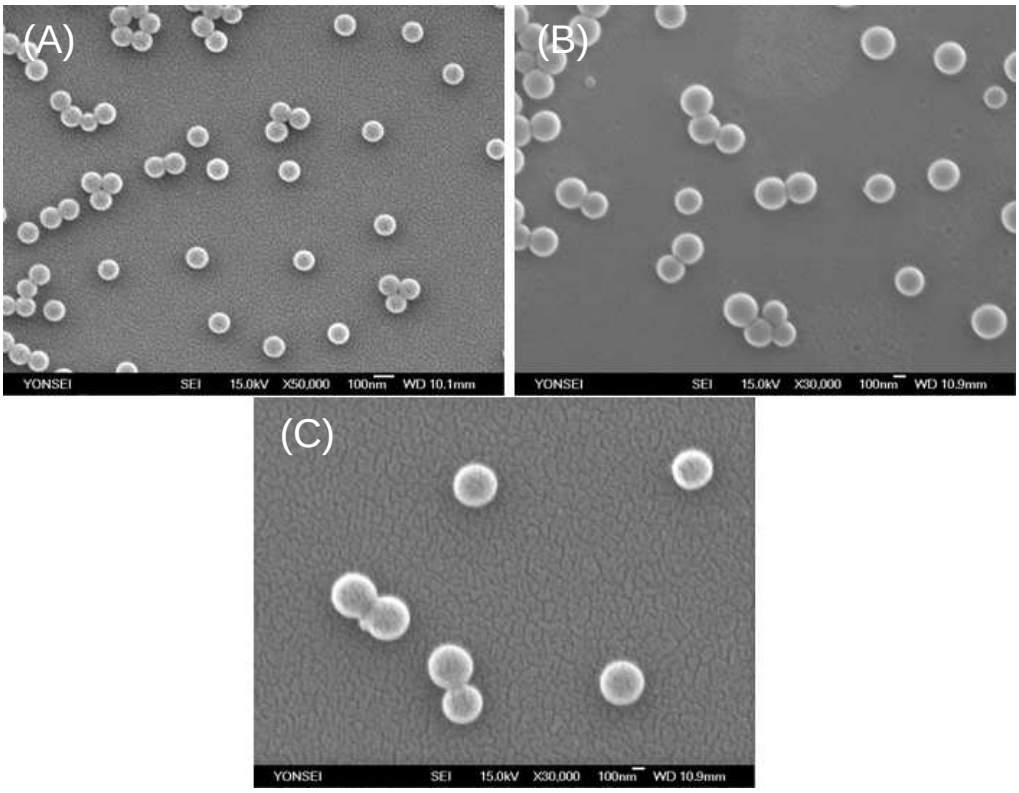


Fig. 15. SEM photographs of HPMC-g-poly(EA/MMA); EA-MMA (A) 0.05 mol (x50,000), (B) 0.15 mol (x30,000) and (C) 0.25 mol (x30,000)

2.5. Mechanical Properties of HPMC-g-poly(EA/MMA) Films

The results of tensile strength and hardness for films made from HPMC-g-poly(EA/MMA) are shown in Fig. 15 and 16. The films were made of HPMC-g-poly(EA/MMA) and HPMC in the ratio of 4:1. The results showed that the more HPMC was added, the higher the values of both tensile strength and hardness obtained, because tensile strength and hardness of poly(EA-co-MMA) is lower than HPMC. The soft segment decreases as the amount of added monomer increases. The hardness of 25% is higher than 0%, because EA-MMA gives plasticity

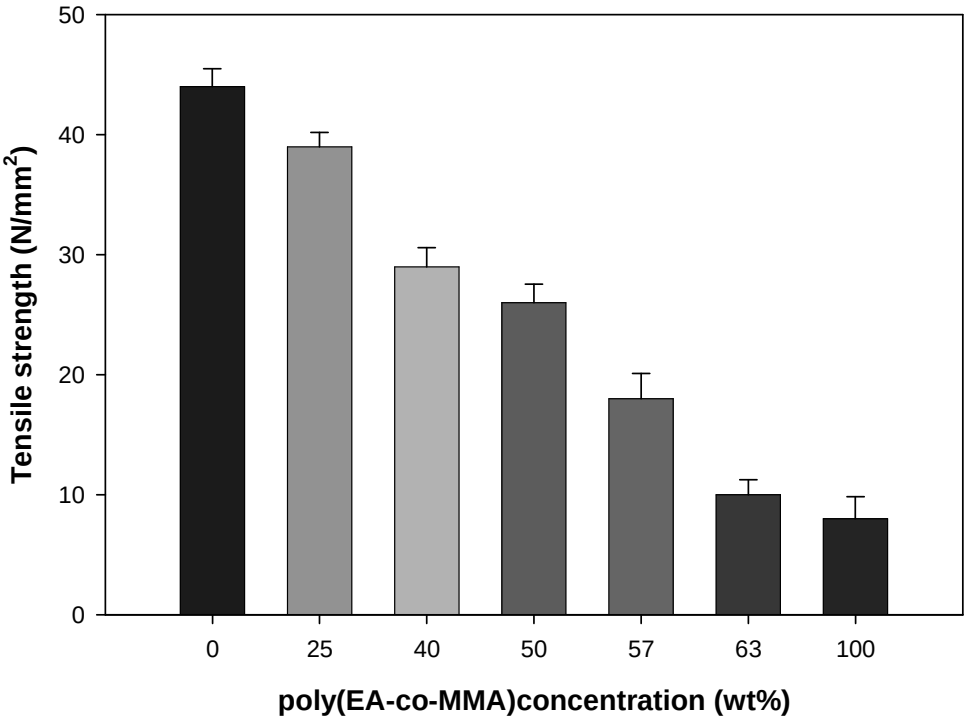


Fig. 16. Tensile strength of HPMC-g-poly(EA/MMA), HPMC and poly(EA-co-MMA)

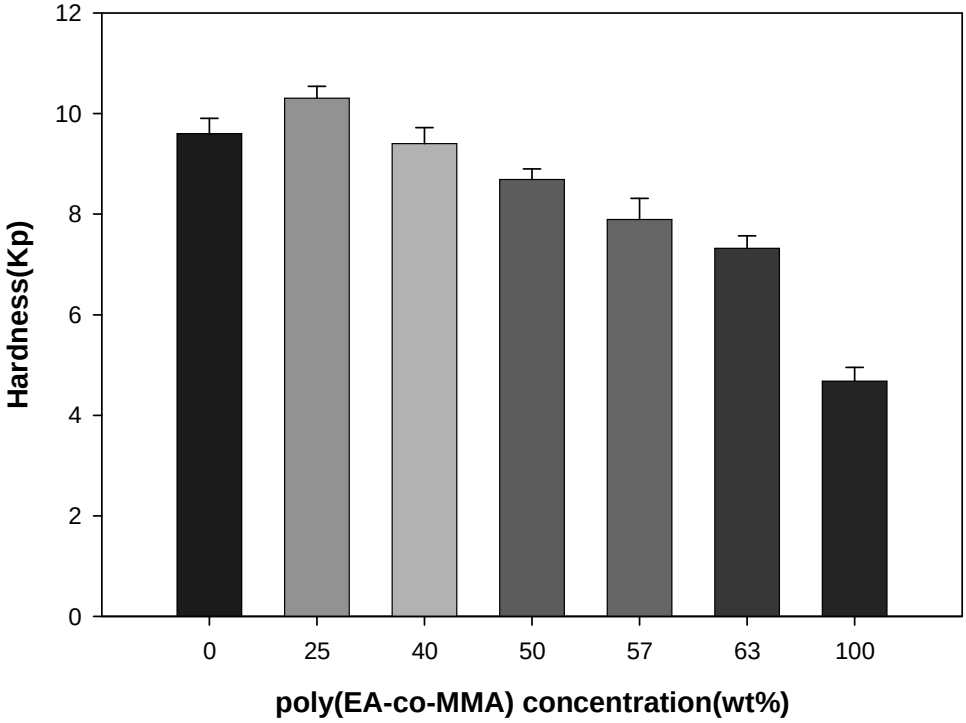


Fig. 17. Hardness of HPMC-g-poly(EA/MMA), HPMC and poly(EA-co-MMA)

2.6. Dissolution profile for controlled release

The dissolution profiles of HPMC-g-poly(EA/MMA) were presented in Fig. 17. When coating tablets were dropped into the water, dissolution started. Table 6 shows the times at of which the tablets were dissolved to 80%. The dissolution ratio increased rapidly for the first 60 minutes but then leveled off. The lag time of poly(EA-co-MMA) was reduced to almost 1 hour. When fast efficient dissolution is needed, these were the method of choice. The time at which the tablets were dissolved to 80% decreased as the amount of added monomer decreased. Controlling the amount of monomer controls the dissolution time.

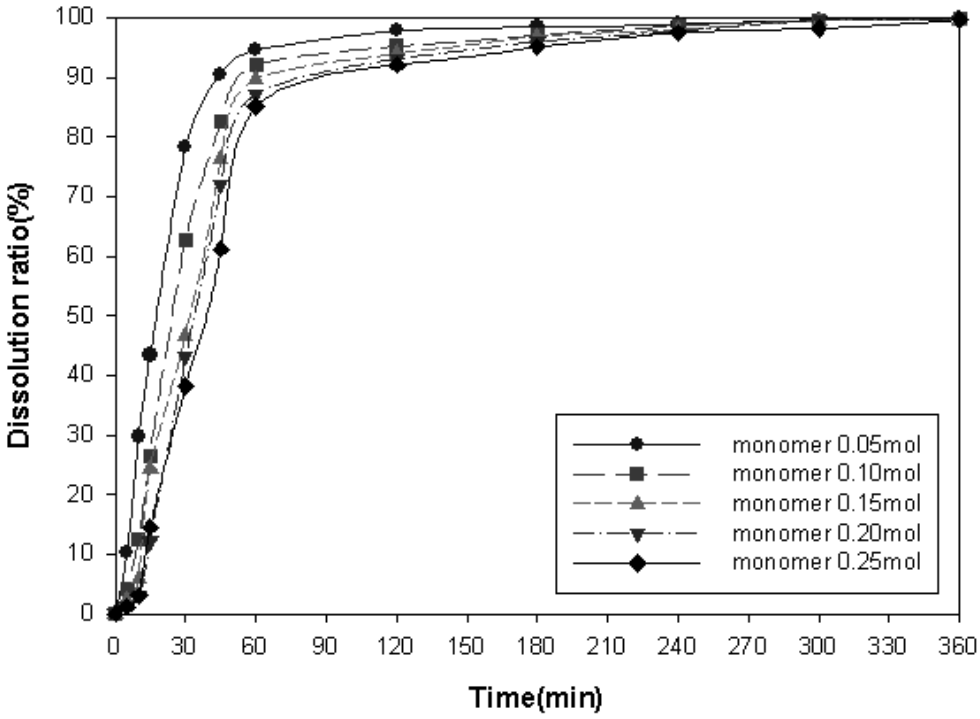


Fig. 18. Dissolution profile of HPM-g-poly(EA/MMA) at water.

Table 6. The times at of which the tablets were dissolved to 80%.

Monomer (mol)	Time of 80% dissolution (min)
0.05	**31**
0.10	**43**
0.15	**46**
0.20	**48**
0.25	**53**

Ⅳ. CONCLUSIONS

HPMC-g-poly(EA/MMA) was synthesize using Hydroxypropyl methylcellulose (HPMC), ethyl acrylate (EA), methyl methacrylate (MMA) and ceric ammonium nitrate (CAN).

The synthesis of HPMC-g-poly(EA/MMA) was carried out by ceric ammonium nitrate (CAN) induced redox polymerization in homogeneous aqueous medium.

When just one OH group is oxidized, the final conversion rate of the reaction has the highest value. When the two or more OH groups are oxidized, hydrophobic chains are generated on two or more sides which give rise to aggregation and restraint of chain-growth. Among these four OH groups in HPMCP, only one OH group should be oxidized by a proper amount of CAN before adding MMA and EA. In response to the attaching of a monomer to oxidized O− in HPMC, the hydrophobic portion would increase so that it enables HPMC to form micelle. When the amount of HPMC is lower than that of CAC, HPMC will not be able to independently form micelles. When the MMA and EA remaining in water penetrate into the micelle, particles formed.

The CH_2 peak in the 2950-2980 cm^{-1} range was used as an internal standard. After completion of the reaction, the intensity of the OH peak at 3100-3600 cm^{-1} confirmed that, of the four OH groups in HPMCP, only one should be

oxidized by proper amount of CAN. Appearance of the C=O absorption peak at 1650-1755 cm^{-1} in FT-IR spectrum indicates a reaction with monomer(EA and MMA) and O^- radical.

The glass transition temperature decreases as the amount of added monomer increases.

When more than 0.07mol of monomer was added, on the other hand, there is little change in the number of micelles due to the regular CAC. In this case, the more monomer that was added, the bigger the particle that was formed because the monomer is used for making particles. When the amount of added monomer is 0.05mol, particles don't have sufficient monomer to grow.

The films were made of HPMC-g-poly(EA/MMA) and HPMC in the ratio of 4:1. The results showed that the more HPMC was added, the higher the values of both tensile strength and hardness obtained, because tensile strength and hardness of poly(EA-co-MMA) is lower than HPMC. The soft segment decreases as the amount of added monomer increases. The hardness of 25% is higher than 0%, because EA-MMA gives plasticity

When coating tablets were dropped into the water, dissolution started. The dissolution ratio increased rapidly for the first 60 minutes but then leveled off. The lag time of poly(EA-co-MMA) was reduced to almost 1 hour. When fast efficient dissolution is needed, these were the method of choice. The time at which the tablets were dissolved to 80% decreased as the amount of added

monomer decreased. Controlling the amount of monomer controls the dissolution time.

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국 문 요 약

유화중합에서 하이드록시프로필 메틸셀룰로오스 수지로 강화시킨 폴리(에틸 아크릴레이트-메틸 메타크릴레이트) 나노입자의 합성

폴리(에틸아크릴레이트-메틸 메타크릴레이트) (poly(EA-co-MMA)는 서방성 코팅 물질로 쓰이는 대표적인 물질이다. 특히, 2000 년 이후 수계 코팅으로 약물 코팅의 추세가 바뀌면서 그 사용량이 늘고 있다. 그러나 poly(EA-co-MMA)의 필름은 잘 부셔지고 약물 용출 시 지연시간이 있다는 단점이 있다. 반면에 하이드록시프로필 메틸셀룰로오스 (HPMC)는 셀룰로오스 고분자로서 필름 특성이 우수하고 안정성이 뛰어난 장점이 있으나, 유기용매를 사용한 코팅에 적용해야 한다는 단점을 가지고 있다.

이번 연구에서 HPMC 수지로 강화시킨 poly(EA-co-MMA) 나노입자를 합성하였다.

제조 후 FT-IR 을 이용하여 합성 여부를 판단하였고, DSC 를 통하여 유리전이온도를 측정하였다. SEM 으로 입자의 형태를 관찰하였다. DLS, CHDF 을 통하여 입자 크기를 측정하였고, UTM 을 이용하여 인장강도와 경도를 측정하였다.

FT-IR 을 통하여 입자가 원하는 대로 합성된 것을 알 수 있었고, 유리전이온도는 단량체의 함량이 높아질수록 낮아지는 것을 볼 수 있었다. 입자 크기는 단량체의 양이 증가 할수록 커졌으나 0.05 몰의 단량체를 넣었을 때는 마이셀을 만들기 위해 단량체가 모두 소비되어 입자가 충분히 성장하지 못하여 입자 크기가 다른 농도에 비해 매우 작은 것으로 추정된다. 0.05 몰 이상에서는 CAC 의 변화량이 작아 입자 수의 변화가 크지 않아 단량체가 첨가 될수록 입자 크기가 커지는 것을 볼 수 있었다. 인장강도와 경도는 단량체의 농도가 진해 질수록 작아지는 경향을 보였다. 합성된 입자를 약물에 코팅하여 분해 실험을 실시한 결과 80%이상 분해 되는데 단량체의 양에 따라 30 분~50 분이 걸렸다. 이로써 기존 poly(EA-co-MMA)에 비하여 1 시간 가량의 지연시간을 줄였고 단량체의 양을 조절하여 원하는 시간의 분해 속도를 가지는 입자를 합성 할 수 있다.

이로써 인장강도와 경도를 향상시키고 약물 방출 시 지연시간을 줄인 입자가 잘 합성된 것을 볼 수 있었다.

핵심되는 말: 하이드록시프로필 메틸셀룰로오스, 하이드록시프로필 메틸셀룰로오스 수지 강화, 산화환원중합, 서방성